



Original Article

Prevalence of familial hypercholesterolemia in premature coronary artery disease patients admitted to a tertiary care hospital in North India



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ABSTRACT

Aims: The prevalence of premature coronary artery disease (CAD) in India is two to three times more than other ethnic groups. Untreated heterozygous familial hypercholesterolemia (FH) is one of the important causes for premature CAD. As the age advances, these patients without treatment have 100 times increased risk of cardiovascular (CV) mortality resulting from myocardial infarction (MI). Recent evidence suggests that one in 250 individuals may be affected by FH (nearly 40 million people globally). It is indicated that the true global prevalence of FH is underestimated. The true prevalence of FH in India remains unknown.

Methods: A total of 635 patients with premature CAD were assessed for FH using the Dutch Lipid Clinic Network (DLCN) criteria. Based on scores, patients were diagnosed as definite, probable, possible, or no FH. Other CV risk factors known to cause CAD such as smoking, diabetes mellitus, and hypertension were also recorded.

Results: Of total 635 patients, 25 (4%) were diagnosed as definite, 70 (11%) as probable, 238 (37%) as possible, and 302 (48%) without FH, suggesting the prevalence of potential (definite + probable) FH of about 15% in the North Indian population. FH is more common in younger patients, and they have lesser incidence of common CV risk factors such as diabetes, hypertension, and smoking than the younger MI patients without FH (26.32% vs.42.59%; 17.89% vs.29.44%; 22.11% vs.40.74%).

Conclusion: FH prevalence is high among patients with premature CAD admitted to a cardiac unit. To detect patients with FH, routine screening with simple criteria such as family history of premature CAD combined with hypercholesterolemia, and a DLCN criteria score >5 may be effectively used.

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1. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder, likely to cause premature coronary artery disease (CAD) and peripheral vascular disorders in patients who inherit the mutant gene and leads to death in some patients.¹ Elevated levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and external manifestations such as tendinous xanthoma and arcus cornealis are characteristic findings in patients with FH. Tendon xanthomata (TX) are widely regarded as a specific physical sign.

FH is primarily caused by genetic mutation in one of the genes for (i) the LDL receptor (LDLR), (ii) apolipoprotein B100 (ApoB), and (iii) proprotein convertase subtilisin/kexin 9 (PCSK9). Individuals

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with mutations of the genes could be heterozygous and homozygous in nature. Majority of patients have heterozygous familial hypercholesterolemia (HeFH), whereas homozygous familial hypercholesterolemia (HoFH) is less prevalent. The extremely rare recessive form of hypercholesterolemia is autosomal recessive hypercholesterolemia which is caused by homozygosity for mutations in the gene encoding the LDLR adaptor protein 1.² Historically, untreated HeFH begins to manifest its clinical consequences in the fourth decade of life in men and fifth decade in women. Patients with HoFH, however, may suffer significant cardiovascular (CV) events as early as in the first decade of life. By early adulthood, these patients without treatment have 100 times greater mortality risk from CV disease resulting from coronary atherosclerosis or supravalvular aortic valve calcification than those without FH.³

The risk of premature CAD is preventable or reversible through early detection and treatment of hypercholesterolemia.⁴ The UK National Institute of Health and Care Excellence guideline has recommended family screening of patients with FH as it will identify many young individuals with a diagnosis of FH who are clinically asymptomatic.⁵

It is regrettable that FH still remains underdetected and undertreated in most countries.⁶ Prevalence of FH heterozygotes by the World Health Organization is estimated to be 1:250, whereas that of HoFH is 1:1,000,000. However, recent studies suggest the prevalence is vastly underestimated.⁷ Owing to India's remarkable population size, it is home to a significant number of FH patients, with very limited information about prevalence of FH in Indian subjects.⁸ Most of our current knowledge on FH stems from studies conducted in the West. Therefore, there is a tremendous need for further research, to determine the true prevalence of FH in India. In the present study, we investigated the prevalence of HeFH using the Dutch Lipid Clinic Network (DLCN) criteria for diagnosis of FH in patients with premature CAD admitted to the Department of Cardiology, Sir Ganga Ram Hospital, New Delhi.

2. Methods

All consecutive patients of acute coronary syndrome or chronic stable angina at an age of <55 yrs in men and <60 yrs in women admitted from May 2016 to May 2018 in the Department of Cardiology at Dharma Vira Heart Center, Sir Ganga Ram Hospital were studied. Patients with advanced liver/kidney disease, cancer, and hypothyroidism and pregnant and lactating women were excluded from the study. Medical history and clinical data were collected prospectively by attending physicians through direct interview with patients and from available medical records. Blood samples for serum lipid profile were collected in either fasting or nonfasting state at the time of admission. The samples were sent for biochemical analysis for estimation of LDL-C, total cholesterol, very low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides.

All patients were assessed for FH using the DLCN criteria. DLCN is a simple clinical, practical tool which is endorsed by many guidelines worldwide, such as the European Society of Cardiology, the National Lipid Association in the USA, the International FH Foundation, and the European Atherosclerosis Society. This includes scoring based on the clinical history, family history, physical examination, LDL-C levels, and DNA analysis (Table 1).⁹ Scores assigned in each group are then added. If a patient scores more than eight points, he/she is diagnosed as a 'definite' case of FH, whereas, if the patient scores between six and eight points, the diagnosis is 'probable' and any score between 3 and 5 points is termed as 'possible' FH and score <3 was considered as no FH. Other CV risk factors known to cause CAD such as smoking, diabetes mellitus, and hypertension were also recorded.

In our study, majority of enrolled CAD patients who did not exhibit hypercholesterolemia were already on statin therapy. In such cases, correction factor was applied to get the prestatin treatment lipid levels to calculate the DLCN points. The correction differs based on the statin prescribed. The LDL-C correction factor for patients on cholesterol lowering medication proved to be useful because patients referred for evaluation were often on lipid-lowering medication and records of the pretreatment values for LDL-C were not always available. The correction factors were developed from the analysis of 71 original articles.¹⁰

For 5, 10, 20, and 40 mg of rosuvastatin, the adjustment factor will be 1.8, 1.9, 2.1, and 2.4, respectively. Similarly, for 10, 20, 40, and 80 mg of atorvastatin, the adjustment factor will be 1.6, 1.8, 2.0, and 2.2, respectively, and, for 10 mg of ezetimibe, LDL-C adjustment factor will be 1.2.

For example, adjusted cholesterol = actual measurement X cholesterol adjustment factor for medication/dose as given by DLCN.

Based on the DLCN criteria, patients were then classified into four groups: definite FH, probable FH, possible FH, and no FH.

On physical examination, all the patients below the age of 45 years were screened for corneal arcus which appears as a single greyish ring parallel to the limbus, and it develops because of deposition of cholesterol, phospholipids, and triglycerides. As the age progresses, it may be difficult to diagnose it from arcus senilis. Corneal arcus when observed in patients younger than 45 years has high diagnostic value.⁹ The lipid deposition process across tissues is presumably similar enough, and this is the reason why looking into the eye might provide us with some clue of what is happening in the coronaries.

Detailed family history of parents, siblings, and children was collected as per the proforma and collated using Microsoft Excel. Analysis of the data was performed using SAS (version 9.x). Data were compared using unpaired *t* tests and chi-square tests. The study was approved by the Institutional Ethics Committee of Sir Ganga Ram Hospital, New Delhi.

3. Results

A total of 635 patients were included. Baseline characteristics of the patients at the time of enrollment are summarized in Table 2. Patients were predominantly men (78.74%); the average age observed was 46.39 ± 7.35 years at enrollment. Untreated LDL-C levels on average were 135.10 ± 43.43 mg/dL. DLCN score average was 3.39 ± 2.15 points. About 37.95% of patients were smokers, 40% had diabetes mellitus, and 27.72% had hypertension. About 7.72% of patients had previous CAD, and 46.85% of patients reported family history of premature CAD. Tendinous xanthoma was observed in one patient (0.19%) and arcus cornealis in 53 patients (8.35%).

Table 3 shows the patient characteristics and prevalence of FH in different categories based on DLCN criteria score. About 3.93% of patients had definite FH, 11.02% had probable FH, with combined prevalence of probable/definite FH (potential FH) being 14.96%.

Probable/definite FH was more common in those with CAD onset aged <50 years, compared with those aged 50–60 years (13.85% vs. 1.10%).

The prevalence of diabetes, hypertension, and smoking is higher in patients without FH than in those with FH (42.59% vs. 26.32%; 29.44% vs. 17.89%; 40.74% vs. 22.11%). Patients already on statin therapy are proportionately more in patients with FH than in patients without FH (58.94% vs. 7.22%). LDL correction was applied in 15% patients to get the untreated LDL levels (Table 4).

Arcus cornealis is a relatively nonspecific diagnostic sign. Overall arcus cornealis was present in 8.34% (53) of patients with premature CAD (all below 45 years), whereas, among potential FH,

Table 1
Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolemia.

Criteria	Points
Family History	1
First-degree relative with known premature (<55 years in men; < 60 years in women) coronary and vascular disease or First-degree relative with known LDL-C level above the 95th percentile	
First-degree relative with tendinous xanthomata and/or arcus cornealis or children aged less than 18 years with LDL-C level above the 95th percentile	2
Clinical history	
Patient with premature (<55 years in men; < 60 years in women) coronary artery disease	2
Patient with premature (<55 years in men; < 60 years in women) cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
Cholesterol levels mg/dl (mmol/liter)	
LDL-C \geq 325 mg/dL	8
LDL-C 250–329 mg/dL	5
LDL-C 190–249 mg/dL	3
LDL-C 155–189 mg/dL	1
DNA analysis	
Functional mutation in the LDLR, ApoB, or PCSK9 gene	8
Diagnosis (diagnosis is based on the total number of points obtained)	
Definite familial hypercholesterolemia >8	
Probable familial hypercholesterolemia 6–8	
Possible familial hypercholesterolemia 3–5	

LDL-C, low-density lipoprotein cholesterol; LDLR, LDL receptor; ApoB, apolipoprotein B100; PCSK9, proprotein convertase subtilisin/kexin 9. This information is adapted from the World Health Organization, 1999 (WHO publication no. WHO/HGN/FH/CONS/99.2).¹¹

Table 2
Baseline characteristics of all patients enrolled.

Baseline characteristics (N = 635)	Mean \pm SD
Age at admission in years	46.39 \pm 7.35
Total cholesterol	172.46 \pm 36.77 mg/dl
LDL-C	135.10 \pm 43.43 mg/dl
HDL-C	33.26 \pm 6.88 mg/dl
Triglycerides	141.05 \pm 44.65 mg/dl
	n (%)
Dyslipidemia	91 (14.33)
Smoking	241 (37.95)
Diabetes mellitus	564 (88.82)
Hypertension	176 (27.72)
Past CAD	49 (7.72)
Family history, premature CAD	297 (46.85)
Arcus cornealis	53 (8.35)
Tendon xanthoma	1 (0.16)
Angina	564 (88.82)

SD, standard deviation; CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Table 3
Prevalence of FH and patient characteristics based on DLCN criteria score in the enrolled population.

	Definite FH	Probable FH	Possible FH	No FH
Total patient (n = 635)	25 (3.93%)	70 (11.02%)	238 (37.48%)	302 (47.55%)
Mean age (years)	40.04	42.50	44.60	49.23
Male (n %)	24 (96.0)	53 (75.71)	190 (79.83)	233 (77.15)
Female (n %)	1 (4.0)	17 (24.29)	48 (20.17)	69 (22.85)
Prevalence (%)	3.93	11.02	37.48	47.55
Diabetes (40.50%)	4 (16.0)	21 (30.00)	78 (32.77)	152 (50.53)
Smoking (37.98%)	4 (16.0)	17 (24.29)	71 (30.25)	148 (49.01)
Hypertension (28.10%)	2 (8.0)	15 (21.43)	58 (24.37)	101 (33.44)
Mean LDL (mg/dl)	237.44	184.63	137.46	113.29
Arcus cornealis	22 (88%)	31 (44.28%)	0	0
On Statin Therapy	10	46	37	2

LDL, low-density lipoprotein; FH, familial hypercholesterolemia.

it was present in 56.38% of patients (53/94). Arcus cornealis was present mainly over the upper pole and less often in the lower pole of the cornea in semicircular shape, and the whole cornea was involved in very few patients.

Although, in the present study, genetic testing was not carried out, in another study of 100 FH patients (definite, probable, possible) who were diagnosed using DLCN criteria from our center, genetic testing was also performed and it was found that 47% of patients had pathogenic variants in LDLR, ApoB100, and PCSK9 genes (Setia et al, 2018, under publication).

4. Discussion

4.1. FH is not rare

The present study is the first one to show a high prevalence of FH in premature CAD (about 15%). To the best of our knowledge, there are no reported large studies of FH or its epidemiology and natural history from India. A number of studies in India have been carried out to study the lipid profile in acute coronary syndrome in India, but there has been little mention of FH in these publications. Only one previous study, which described clinical profiles and treatment patterns of 997 patients with premature CAD, just briefly mentioned that there was 1.3% prevalence of possible FH in the study population.⁸ Not only this, a previous study from Tamil Nadu has shown that even the awareness and knowledge of FH among primary care physicians remains suboptimal.¹¹ Thus, there are huge gaps among Asian countries about the knowledge, frequency of occurrence, and care of FH.

The present study showed that the prevalence of potential (definite + probable FH) FH in premature CAD patients is about 15%, which is comparable with an estimate of 14.3% (95% confidence interval, 9.0%–19.5%) prevalence in an Australian study of 175 patients admitted in coronary care unit with CAD at age < 60 years.¹² Patients were diagnosed based on phenotypic DLCN criteria. In the Copenhagen General Population Study, 98,098 individuals were genotyped for LDLR and ApoB mutations and it was found that FH-causing mutations estimated to occur in 1:217 in the general population and are identified by definite or probable phenotypic diagnosis of FH based on the DLCN criteria.¹³ In a recent study of 1602 adolescents from the Western Australian Pregnancy Cohort Study, it was found that FH was common in adolescents, with an estimated prevalence of 1:267.¹⁴

In EUROASPIRE IV study conducted in 7044 coronary patients, the reported prevalence of potential FH was 8.3%. It was shown that the prevalence was inversely related to age, that is, 1:5 in those with coronary heart disease (CHD) <50 years of age.¹⁵ Our results are compatible with the European data from 24 countries.

In our study, 298 (47%) patients had a family history of premature CAD, which is comparable to that reported by Pang et al¹² from

Table 4
Relation of age with FH clinical diagnosis.

FH	No. of patients who are of age 50 or <50 years	No. of patients who are >50 years of age
Definite	25	0
Probable	63	6
Possible	179	57
No	149	154

FH, familial hypercholesterolemia.

Australia who showed that 46.3% of patients had family history of premature CAD. Our study depicts that clinical FH is common and associated with markedly earlier age of coronary event. First index event provides an opportunity for earlier identification of FH in the family.

In the present study, FH patients with premature CAD exhibited single-vessel disease in the probable and possible FH group than in the definite FH group. Multivessel disease was more frequent in the potential FH group (73.40% [69/94]) than in the possible FH group (49.15% [116]) ($p < 0.00001$). Rerup et al¹⁶ showed that, in patients with acute coronary syndrome (ACS), the rate of recurrent myocardial infarction was higher in patients with FH than in those who did not have FH.¹⁶ Zafirir et al¹⁷ showed that there were recurrent coronary revascularizations over time in FH patients with CAD.¹⁷

4.2. FH is easily identifiable

FH diagnosis in patients affected with premature CAD is underrecognized.¹⁸ Although there are no universally accepted criteria for the diagnosis of FH, we used DLCN criteria and found that FH can be easily identified by the use of simple, inexpensive, and noninvasive DLCN criteria. The information produced is reliable. In the present study, the presence of conventional risk factors is less common in patients with CAD with FH than in CAD patients without FH. This indicates that traditional risk factors are not sufficient for risk prediction in this young group of patients, rather there is a genetic component in causation of CAD in FH patients.

DLCN criteria as well can be used to make a clinical diagnosis of FH in primary care settings. Patient with a DLCN score greater than five should be referred for DNA testing. To confirm a diagnosis of FH, health-care professionals should undertake two measurements of LDL-C concentration for biological and analytical variability. As per the National Institute for Health and Clinical Excellence (NICE) guidelines, FH should be suspected in adults with high LDL-C and a family history of premature coronary heart disease. As per these guidelines, the absence of physical signs such as tendinous xanthoma and arcus cornealis in young people does not exclude a diagnosis of FH.⁵

Although tendon xanthomas are considered a classical physical sign of FH, however, they may be absent or difficult to diagnose with confidence, even by experienced lipid clinicians. In the our study, TX were present in only one patient, in contrast with the study by Haralambos et al¹⁰, which showed that prevalence of TX is about 43% in a cohort of mutation-positive individuals.¹⁰ The significant difference in this finding is difficult to explain and requires further studies in Indian subsets. The presence of TX in genetically confirmed FH patients is associated with a significant increase in CV risk.¹⁹

Haralambos et al¹⁰ observed corneal arcus in 33 (34%) of 96 patients.¹⁰ This is consistent with previous studies which showed that, in clinical practice, corneal arcus is commonly linked with FH and corneal arcus was more commonly detected than tendon xanthoma. The presence of arcus cornealis in our study patients

was an important physical finding, which was useful in diagnosis of potential FH (definite and probable).

4.3. Importance of cascade screening

As per the NICE guidelines 2017, cascade testing using DNA testing should be carried out to identify affected first-, second-, and, when possible, third-degree biological relatives of people with a genetic diagnosis of FH.⁵ Alternatively, when genetic testing is not available, nonfasting lipid profile of the family members (siblings and children) is also an effective and simple method to diagnose the carrier. The earlier and timely intervention (lifestyle changes and statin therapy) based on cascade screening can prevent premature CAD in community.

The ideal age of lipid screening among children has been a controversial issue. According to the National Lipid Association Expert Panel on FH, children born with family history of high cholesterol or premature CHD should undergo screening for lipids at age ≥ 2 years.²⁰ Screening before 2 years of age is not recommended. Based on the National Health, Universal screening is best performed between 9 and 11 years of age.^{21,22} As per the National Lipid Association key screening recommendations, FH should be suspected if children, adolescents, or young adults <20 years of age have LDL-C ≥ 160 mg/dl.

Physical findings such as tendon xanthoma at any age, arcus cornealis at the age <45 years, and xanthelasma at the age <25 years strongly suggest FH. Lipid levels should be obtained in these individuals if not already available.

Usage of genetic testing and treatment recommendations based on the research can be used for efficient management of FH.

4.4. Limitations

Our present study has several limitations. First, it was a single-center study. Our hospital, being a tertiary care hospital, receives patients not only from Delhi but also from neighboring states, thereby giving an idea of prevalence in North India. Therefore, these results may not be applicable to the entire diverse population of India. Further studies of more diverse populations from various centers of different regions are required to know the true prevalence of FH in India. Second, the lipid measurements were performed in different laboratories. Interlaboratory variation could have biased the prevalence of FH. In addition, there were patients in whom the LDL-C levels were not measured, but 'untreated LDL-C levels' were estimated using a validated correction formula. The genetic analysis was not performed in our study patients to confirm the diagnosis which could have combined our cases of FH with inherited dyslipidemias, such as polygenic FH which is an important differential diagnosis. Some patients were unaware of their family history of premature CAD, which probably underestimated the true prevalence of FH.

5. Conclusion

It is concluded that prevalence of FH is high among patients with premature CAD admitted to a cardiac unit. To detect patients with FH, routine screening with simple criteria such as family history of premature CAD combined with pretreatment LDL cholesterol of >155 mg/dL and a DLCN criteria score >5 may be effectively used. Cascade testing of close relatives is also crucial for early detection and prevention of CAD among family members. Cardiac units and the staff working there play a major role in the detection and overall care of FH. We suggest that measures should be taken to create awareness about FH as one major cause of young heart attacks, among physicians, nurses, and health-care

professionals. This approach of spreading awareness will be cost effective as compared with losing young lives due to premature heart attacks.

If the large burden of atherosclerotic CV disease associated with FH is to be reduced, then the diagnosis and treatment must begin in early life. “By diagnosing a case of FH, we do not identify a case but a family at risk”.

Conflict of interest

The authors have read the journal's policy and have the following disclosures: J.P.S.S. reports personal fee from Pfizer, AstraZeneca, Novartis, Sanofi, and BMS outside the submitted work. A Mohanty reports personal fee from AstraZeneca, Sun Pharma, and Intas outside the submitted work. R.P. reports personal fee from AstraZeneca, Eris Lifesciences, Boehringer Ingelheim, Novartis, and Torrent outside the submitted work. A Mehta reports personal fee from Pfizer, AstraZeneca, Novartis, Sanofi, and BMS outside the submitted work. B.K. reports personal fee from Lupin, Torrent, and Cipla outside the submitted work. R.R.M. reports personal fee from Sun Pharma and Lupin Ltd. outside the submitted work. S.R.P., M.S., K.M., A Makhija, R.J., B.S.V., S.C.M., and I.C.V. have nothing to disclose.

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